

Low-Dose Risperidone as Adjunctive Therapy for Irritable Aggression in Posttraumatic Stress Disorder

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Abstract: Increased aggressive behavior can occur in association with posttraumatic stress disorder (PTSD). This study tested the hypothesis that low-dose risperidone reduces aggression and other PTSD-related symptoms in combat veterans. Subjects were male combat veterans with PTSD who scored 20 or higher on cluster D (hyperarousal) of the Patient Checklist for PTSD–Military Version (PCL-M). Subjects were randomly assigned to either risperidone or placebo treatment groups. Drugs were administered over a 6-week treatment period in a double-blind manner. Subjects received either risperidone (0.5 mg/day; $n = 7$) or matched placebo ($n = 8$) tablets during the first 2 weeks of the treatment period. The dose of risperidone could then be increased up to 2.0 mg/day on the basis of response. Prerandomization psychotropic regimens were continued. Subjects were evaluated with the PCL-M and the Overt Aggression Scale–Modified for Outpatients (OAS-M). In comparison with placebo treatment, reductions in scores between baseline and the last week of treatment were significantly greater for OAS-M irritability and PCL-M cluster B (intrusive thoughts) subscales and on the PCL-M total scale. These results suggest that low-dose risperidone administration reduces irritability and intrusive thoughts in combat-related PTSD.

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Posttraumatic stress disorder (PTSD) is a common psychiatric disorder among military veterans exposed to combat. Three symptom clusters characterize the persistent responses to the stressor(s): reexperiencing the event (cluster B: intrusive thoughts); avoidance and emotional numbing (cluster C: loss of interest, avoidance); and hyperarousal (cluster D: irritability, hypervigilance). The impaired patterns of arousal seen with high levels of cluster D symptoms are considered one source of the deficits in anger regulation found in combat-related PTSD.¹ Although aggression per

se is not a criterion for diagnosis of PTSD, it is often seen in the disorder. Combat veterans with PTSD, in particular, commonly have problems with impulsiveness, explosiveness, and aggression.²

Pharmacotherapy is necessary for many patients with PTSD because of the distress caused by the severity and persistence of their symptoms. Tricyclic antidepressants and monoamine oxidase inhibitors have moderate efficacy, but selective serotonin reuptake inhibitors (SSRIs) are now generally considered first-line agents in treatment of PTSD.^{3,4} However, SSRIs have not consistently been shown to significantly improve scores on most symptom measures in combat-related PTSD.^{5–9}

When patients are responding partially to medication, the expert consensus guidelines for the treatment of PTSD recommend adding another medication as an adjunct rather than switching to a different medication. Recommendations for specific adjunct medications are based on the initial medication, as well as the nature and severity of persistent symptoms. When these problems are irritability, anger, or aggressive behavior, the most commonly recommended adjunctive medication is a mood stabilizer, with atypical antipsychotics recommended as second-line therapy.

Two studies have shown effects on irritability,^{5,6} but no placebo-controlled clinical trial has shown that any medication can reduce aggression in combat-related PTSD. Findings of benefits from risperidone on pathological aggression in schizophrenia¹⁰ and other disorders,¹¹ as well as case reports of reductions in aggression when used in PTSD,^{12,13} suggest that risperidone could have a therapeutic role in PTSD. To test this hypothesis we conducted a double-blind, placebo-controlled, randomized trial of the efficacy and safety of low-dose risperidone as an adjunctive medication in reducing the symptoms of PTSD.

METHODS

Subjects

Sixteen patients at the Veterans Affairs Boston Healthcare System (VABHS) were recruited. One subject in the risperidone group dropped out before completing the second week because of an episode of urinary retention. The study was conducted with approval from the VABHS Human Subjects Subcommittee. Subjects provided voluntary

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consent prior to admission into this investigation. Subjects were male combat veterans who met the DSM-IV criteria for PTSD rated with the Clinician-Administered PTSD Scale¹⁴ and scored ≥ 20 on the cluster D subscale (hyperarousal) of the Patient Checklist for PTSD–Military Version (PCL-M).¹⁵ Comorbid diagnoses were made with use of the Structured Clinical Interview for DSM-IV.

Patients were excluded if they had a history of schizophrenia, bipolar disorder with psychotic features, or organic mental disorder or had ever been prescribed an antipsychotic medication. Subjects with diagnosed substance dependence had to be in remission for 1 year prior to study entry. Patients' psychotropic medication or individual or group therapy that was ongoing at the beginning of the study continued unchanged.

Treatment and evaluation

Patients were randomized to double-blind treatment with risperidone or placebo. After random allocation to treatment, patients started taking the medications and were seen after treatment weeks 2, 4, and 6. Patients received study medication at a dosage of 0.5 mg/day for the first 2 weeks. After weeks 2 and 4 the dosage could be increased on the basis of clinical response and the presence of side effects, up to a possible total dose of 2.0 mg/day.

Instruments

Overt Aggression Scale–Modified for Outpatients (OAS-M).

The OAS-M is a systematic interview administered by a clinician. It has three subscales that measure aggression, irritability, and suicidality.¹⁶ Aggression subscale scores are frequency/severity assessments of overt aggressive behavior for the past week. This subscale has no ceiling and is weighted to increase with the seriousness of the aggression. The irritability subscale assesses both subjective and overt irritability.

Patient Checklist for PTSD–Military Version (PCL-M).

The PCL-M is a self-reporting questionnaire that assesses symptoms of PTSD related to military experiences. The questionnaire is divided into three subscales measuring cluster B (intrusive thoughts), cluster C (avoidance), and cluster D (hyperarousal). Subjects are asked to rate the degree of difficulty with each symptom in the past month with use of a 5-point Likert scale.

Secondary measures of anger and hostility given at baseline and week 6 include the Buss-Durkee Hostility Index (BDHI),¹⁷ the Spielberger State-Trait Anger Scale (the state version [STAS-S] and the trait version [STAS-T]),¹⁸ and the State-Trait Anger Expression Inventory (STAS-AX).¹⁹ Depression was measured with the self-rated Beck Depression Index (BDI)²⁰ and anxiety with the self-rated

Beck Anxiety Index (BAI).²¹ The Dissociative Experiences Scale (DES) measured symptoms of dissociation.²²

Data analysis

Mean group ages, educational levels, and dosages were compared by one-way ANOVA.²³ Baseline data from each instrument were assessed with the Shapiro-Wilk statistic as a test of normality. Results for scales that were determined to have normally distributed baseline data (BDI, BAI, STAS-AX, STAS-T, and STAS-S) were analyzed with use of a repeated two-way ANOVA, with time as the within-week factor and drug treatment as the between-group factor. One-way repeated measures ANOVAs were used to compare within-group scores across time. Group comparisons for normally distributed data at baseline were done with use of one-way ANOVAs. Comparisons of baseline values for scales that were determined not to have normally distributed data (DES, BDHI) were made with use of the median test.²³ Change scores (week 6 minus baseline) for scales for which baseline data were not normally distributed were evaluated with a median test. This is a non-parametric test that assesses whether data obtained from two groups are from populations with the same median. The Wilcoxon sign-rank test was used to determine if within-group changes were significant. Results were considered significant at a level of $p < 0.05$.

RESULTS

Fifteen subjects completed the full 6-week trial. All primary traumatic events leading to the diagnoses of PTSD were combat-related: two subjects were Gulf War veterans and the remainder were Vietnam War veterans. Twelve subjects were white, two were black, and one was Hispanic. The 7 subjects in the risperidone group had a mean age of 48.9 years (standard deviation [SD], 8.3) and a mean education level of 11.4 years (SD, 2.0). For the 8 placebo subjects the mean age was 53.5 years (SD, 3.0), with a mean education level of 11.9 years (SD, 2.3). Treatment groups did not differ significantly with respect to mean age ($F [1, 13] = 2.22$; $p = 0.16$) or educational level ($F [1, 13] = 0.2$; $p = 0.66$). At baseline there were no significant between-group differences for either the primary or secondary outcome measures. The mean dose of risperidone was 0.57 mg (SD, 0.13) for the active treatment group. Subjects in the placebo group took tablets equivalent to a 0.62-mg (SD, 0.19) dose of risperidone. Mean "doses" for the two experimental groups were not significantly different ($F [1, 13] = 0.38$; $p = 0.5$).

Every subject had at least one comorbid diagnosis. In the risperidone group, current psychiatric diagnoses included major depression ($n = 4$), dysthymic disorder ($n = 1$), generalized anxiety disorder ($n = 2$), and panic disorder ($n = 1$). Lifetime diagnoses for this group included al-

cohol abuse ($n = 1$), alcohol dependence ($n = 3$), major depression ($n = 2$), and cocaine abuse ($n = 1$). For the placebo group current diagnoses included major depression ($n = 6$), dysthymia ($n = 1$), and generalized anxiety disorder ($n = 1$), and lifetime diagnoses were major depression ($n = 1$) and alcohol dependence ($n = 2$). Concurrent antidepressant medications received by the risperidone group included nefazodone ($n = 6$), trazodone ($n = 3$), and fluoxetine ($n = 1$). This group was also treated with the antianxiety agents alprazolam ($n = 2$), temazepam ($n = 2$), and diazepam ($n = 2$). Antidepressant agents administered to the placebo group included sertraline ($n = 2$), nefazodone ($n = 2$), trazodone ($n = 3$), and paroxetine ($n = 1$). This group was also treated with the antianxiety agents diazepam ($n = 2$), lorazepam ($n = 1$), and buspirone ($n = 2$). One patient was being treated with lithium and one with gabapentin. Adverse events were scored as none, mild, moderate, severe, or life-threatening. The scores for the risperidone group included mild ($n = 4$) and none ($n = 3$). The placebo group scores were mild ($n = 2$), moderate ($n = 1$), and none ($n = 5$).

Table 1 shows the median scores at baseline and median change scores for our two major efficacy measures, the OAS-M and the PCL-M. We found significant differences for the change score (week 6 minus baseline) on the irritability subscale of the OAS-M and on both the cluster B (intrusive thoughts) and total score for the PCL-M. Significant group differences were not detected for the aggression subscale of the OAS-M.

There were no significant between-group differences for the change score on any of the secondary measures.

DISCUSSION

Low-dose risperidone was significantly more effective than placebo in decreasing irritability, as measured by the

OAS-M, intrusive thoughts (cluster B) PCL-M, and total PCL-M scores in a group of combat veterans with severe PTSD, but it was not more effective in reducing measures of anxiety and depression. Other investigators have also found improvement in symptoms of PTSD with use of risperidone as an adjunctive medication. DeFaria et al., in an open-label, flexible-dose trial of adjunctive risperidone in 12 male combat veterans with chronic PTSD, of whom 11 had psychotic features,²⁴ reported significantly lower scores at endpoint on cluster B (intrusive thoughts) of the CAPS. On their other efficacy measure, the Positive and Negative Syndrome Scale (PANSS), the positive symptoms subscale and the total score were significantly different at endpoint. Bartzokis et al. reported that risperidone was significantly more efficacious than placebo on the CAPS-total and the CAPS-D subscale (hyperarousal) as well as on the HAM-A and the PANSS-P.²⁵

Our results suggest that there is a role for risperidone in reducing irritability and intrusive thoughts in combat-related PTSD. It is uncertain whether the effects of risperidone on these symptoms are due to the actions of this drug alone or the combination of risperidone and antidepressants. Despite our use of a double-blind, placebo-controlled design, limitations of our study include a small sample size and lack of complete balance with respect to comorbid diagnoses and use of concomitant medications. The results of this trial suggest that future studies with larger samples should examine the efficacy of risperidone as monotherapy and as combination therapy with antidepressants for combat-related PTSD.

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TABLE 1. Treatment response assessed by primary efficacy measures

Scale	Risperidone		Placebo		<i>p</i>
	Baseline	Change	Baseline	Change	
OAS-M aggression	13.0	-12.0†	11.0	-8.0	0.80
OAS-M irritability	7.0	-2.0†	6.0	-1.0	0.04*
OAS-M suicidality	0.0	0.0	1.5	-1.0†	0.08
OAS-M total	19.0	-17.0†	18.5	-9.5	0.79
PCL-M cluster B	23.0	-4.0†	21.5	0.0	0.001*
PCL-M cluster C	27.0	-2.0	26.5	2.0	0.20
PCL-M cluster D	24.0	-2.0	22.5	0.0	0.20
PCL-M total	73.0	-10.0†	72.0	-0.5	0.02*

Median scores for baseline and median change scores (week 6 minus baseline) are shown. OAS-M, overt aggression scale-modified for outpatients; PCL-M, patient checklist for PTSD—military version. *p* values are given for between group comparisons.

*indicates $p < 0.05$ for between group comparisons for differences scores.

†denotes $p < 0.05$ for within group difference scores.

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